REMARKS

Claims 1-17 are pending and have been rejected. Claims 4, 5 and 9-11 are canceled by this amendment. Claims 1, 2, 3, 6-8 and 12-17 are currently amended. Claims 18-52 were canceled previously. Claim 53 has been added based on recitations in original claims 1, 2 and 17. A paragraph on page 2 of the specification has been amended.

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. This amendment adds, changes, and/or deletes claims in this application. With an appropriate, defined status identifier, a detailed listing is presented of all claims that are or were in the application, irrespective of whether the claim(s) remain under examination in the application. After the revisions set forth above, claims 1-3, 6-8, 12-17 and 53 will be pending.

Sequence compliance

The specification has been reviewed for missing sequence identifiers. The examiner cites page 36, line 6, as an example of a missing identifier. However, a sequence identifier already was inserted at this point in the marked-up version of the specification that accompanied the Sequence Listing filed October 15, 2001. Upon review, applicants are amending a paragraph on page 2 to reference both the appended PatentIn program identifiers and the SEQ IDs.

Specification

The requisite statement regarding the clean copy of the specification, forwarded on December 12, 2002, is provided with response.

Claim objections

Claim 17 is subject to objection for improper dependent form. With the present amendment to claim 1, claim 17 is properly dependent.

Section 112 Rejections

Second paragraph

Claims 1-17 are rejected under the second paragraph of Section 112. The claims have been amended to recite "immunogenic" complexes, as in the original claims. This should eliminate any ambiguity. The phrase "derivative or equivalent" has been deleted. Claims 9-11 have been canceled, obviating the stated grounds for rejection in this context.

First paragraph – lack of enablement

Claims 1-8 and 17 are rejected under the first paragraph for lack of enablement. In this regard, she alleges that the specification does not enable "any negatively charged organic molecule, adjuvant or derivative or equivalent thereof electrostatically associated with any charged or positively charged antigen or derivative or equivalent thereof to induce a CTL response." The claims have been amended to eliminate reference to derivatives and equivalents, and claim 1 has been amended to recite that the organic complex comprises a saponin and a sterol. These claim amendments, and the foregoing argument relating the scope of the term antigen, should obviate at least part of the basis for this rejection.

Central to the rejection is the examiner's contention that the claimed invention is enabled, not for all electrostatically associated combinations of a charged antigen and charged adjuvant, but rather only for those combinations exemplified in a working example. While rejections under Section 102 and 103 based on Nakanishi have been withdrawn in the current action, Nakanishi resurfaces as evidence for the allegation of non-enablement. More particularly, while the examiner now agrees that the Nakanishi complex fails to generate a CTL response, she argues that this very fact, coupled with her ongoing position that the complex of Nakanishi *et al.* "clearly falls within the scope of instant claim 1...demonstrate that the scope of the claimed complexes are not enabled for generating a CTL response" (Office Action at page 8).

Forwarded with this response is a Rule 132 declaration by John Cox, one of the named inventors. Dr. Cox explains why Nakanishi *et al.* does ***not***, in fact, describe a complex falling within the scope of claim 1. First, he notes that the examiner's previous assessment of Nakanishi (Action dated 23 May 2001), in which she concluded that "the negatively charged

end of [phosphatidylcholine] would be found in the interior of the vesicle," evidences a misunderstanding of phospholipid structure and, hence, of liposome structure. The examiner was correct in the May 23d Action when she stated that phosphatidylcholine is an amphipathic molecule, but the allegation that a negatively-charged end of this molecule is found in the interior of a liposome was incorrect. Dr. Cox explains that liposomes consist of cholesterol, and one or more phospholipids. In their simplest manifestation, they are a bilayer membrane with the hydrophilic headgroup exposed at the internal and external surface. Each layer of the bilayer is aligned so that the hydrophobic ends meet at the middle of the bilayer and the hydrophilic ends are on the surface. A phospholipid consists of two hydrophobic chains, a phosphate group and a head group. The phosphate group carries a negative charge, while the head group may be positively charged or neutral. Phosphatidylcholine (PC) has *both* a positive (choline) and negative (phosphate) entity exposed at the internal and external surfaces of the membrane, resulting in an overall neutral charge; that is, the liposome will be neutral at *both* its internal and external surface. Phosphatidic acid (PA) lacks a head group and so is overall negative. In either case, the hydrophobic chains point toward the hydrophobic side of each layer, and the phosphate and head group point toward to the hydrophilic surface of the layer.

Dr. Cox notes that Nakanishi used conventional techniques to combine antigen and liposomes. According to such techniques, loading of liposomes is achieved by high pressure agitation, by vortexing or otherwise mixing a lipid film with an aqueous solution of antigen. The loading is very inefficient, as shown by the fact that the external aqueous volume after this process is vastly greater than the encapsulated aqueous volume. No worker in the field prior to the present invention suggested that this inefficiency could be overcome by selecting lipids for preparing liposomes which had a charge suitable for binding the antigen of choice to be loaded. Furthermore, Dr. Cox attests that ***"there is no basis for assuming any sort of electrostatic interaction in Nakanishi."*** Accordingly, the examiner's conclusion, that Nakanishi's complex "clearly falls within the scope of instant claim 1," has been demonstrated to be incorrect.

More particularly, Dr. Cox notes that Nakanishi uses only two antigens, chicken egg albumin (OVA) and beta-galactosidase. Chicken egg albumin has a pI of 4.9, and beta-

galactosidase has a pI of 4.6. Assuming that the antigen and MLV are co-dispersed at 7.6 (the pH stated for the control), both antigens would be negatively charged in Nakanishi. Nakanishi purports to make combinations of these two negatively-charged antigens with negatively-charged, positively-charged and neutral liposomes. This shows that the intention in Nakanishi is not to create an electrostatic interaction. Contrary to the situation in Nakanishi, which does not entail electrostatic interaction, the present invention empowers the manufacture of electrostatically associated complexes. Such complexes do generate a CTL response, as applicants discovered.

The examiner contests the reasonable assumption that the antigen and MLV in Nakanishi would be co-dispersed at the same pH, as was stated for the controls in Nakanishi. She provides no reason why this assumption is unreasonable. Clearly, she cannot contest that both antigens used in Nakanishi would be negatively charged at a pH of 7.6, given that their pIs are 4.9 and 4.6, respectively. Instead, she replaces applicants' reasonable assumption with one of her own, namely, that "the natural, positive charge of some amino acid residues within each of the antigens used in the reference" would equate to a positively charged antigen, which electrostatically associate with the negatively charged particles within the liposome. Yet the fact remains that, at the pH of 7.6, overall charge of the antigen would be negative; hence, the basis for association between liposome and antigen in Nakanishi must be something other than an electrostatic interaction.

In this regard, Dr. Cox expands his explanation of Nakanishi's teaching, by noting its focus on the interaction between liposome and macrophages, and ***not*** the interaction between liposomes and antigen. Thus, Nakanishi's Figure 4 shows that all liposomes, regardless of charge, are able to enhance antibody response. Conversely, Nakanishi shows in Figure 2 and repeatedly states in the text that only positively-charged liposomes are able to induce CTL responses. This was attributed to the fact that only positively-charged liposomes were able effectively to bind to the surface of murine macrophages. Nakanishi does not teach or suggest that charged liposomes can be combined with oppositely-charged antigens to improve association between the two. On the other hand, Nakanishi specifically teaches that only positively-charged liposomes are able to induce CTL responses.

The examiner's allegation that "the scope of the claimed complexes are not enabled for generating a CTL response" also is addressed by Dr. Cox, who provides a detailed discussion of the CTL response, along the lines presented during an earlier interview. Elaboration of the nature of the CTL response was requested by the examiner during a subsequent interview. In addition, Dr. Cox provides both (i) a published paper [Polakos *et al.*, 2001] describing results of studies with the hepatitis C core antigen formulated by the method of the present application and (ii) a report on very recent studies using a hepatitis C polyprotein which is a fusion of five hepatitis C proteins. These clearly refute the examiner's contention that the present invention is not enabled beyond the scope of the working examples, by demonstrating that applicants' teachings can be used to generate electrostatic complexes across the broad class of antigens, and the resulting complexes will induce CTL responses in the subjects to which they are administered.

Finally, Dr. Cox attests that "only minimal experimentation of a routine nature is required to practice the invention with combinations other than those reported in the specification." More particularly, he notes that the specification teaches how to select and make a charged organic complex, how to bring about association between a charged organic complex and a charged antigen and how that association can be increased by modifying either or both of the organic complex and antigen. The specification also teaches ways of testing the resulting association, and shows that when association has been achieved, benefits such as CTL response result. Any necessary experimentation is readily carried out by a skilled technician, and is not undue in this field.

First paragraph – lack of written description

Claims 1-8 and 17 are rejected under the first paragraph for lack of written description. The examiner cites page 9, lines 14-15 as "defin[ing] 'complex' as two or more chemical components that interact with each other. The disclosure does not describe a feature that distinguishes between the complex and the organic complex." The amendments to the claims to recite and "immunogenic" complex should address this concern. This clearly indicates that the immunogenic complex is a complex which, when introduced into an animal, is immunogenic and comprises an organic complex component, the subunits of which are now specified in claim 1. The definition on page 9 cannot be read in isolation but must be

read in light of the fact that the claims actually provide a further descriptive limitation in relation to the nature of the given complex.

The examiner further cites page 12, lines 19-22 as "defin[ing] adjuvant as any substance that potentiates an immune response. Although there is functional language provided for what the adjuvant does, there is no structural definition. The claims do not require that the protein or adjuvant possess any particular distinguishing feature, biologic activity, or conserved structure, except for their respective overall charge." However, the notion of adjuvants and molecules which can function as adjuvants is an extremely well-described and well-known immunological phenomenon which, in terms of specific distinguishing features and biological activity, would be perfectly clear to any immunologist. Nevertheless, without prejudice and in order to advance prosecution, it is proposed to delete reference to "adjuvant" *per se* and to specify that the subject organic complex comprises saponin and a sterol. Support for "saponin" is provided in canceled claim 9, and throughout the specification. Support for "sterol" is provided in the definition of "organic carrier" which runs from page 12, line 1 to page 13, line 4, which recites and incorporates a number of citations providing extensive lists and descriptions which could form part of the organic complex, including sterols, *per se*.

The examiner has raised a similar issue as to the term "protein," asserting that the claims do not require that the protein possess a particular distinguishing feature, biological activity or conserved structure. Applicant notes the term "protein" has now been amended to read "peptide." Support for this amendment is found at page 10, lines 20-24, where the term "protein" is expressly defined to include peptides. The subject protein/peptide is defined in the context of its function as an "antigen." Accordingly, it must exhibit a particular biological activity and structure. The person of skill in the art would understand that an antigen is a molecule which can react with an antibody. Like adjuvant, antigen is an extremely well-defined class of molecule. Thus, the specification, when considered in light of the art, does provide sufficient identifying characteristics for this genus.

For all of the foregoing reasons, reconsideration and withdrawal of the rejections under Section 112, first paragraph for lack of written description and lack of enablement is respectfully requested.

Section 102(b) Rejection

Claims 1-8 and 12-17 are rejected under Section 102(a) based on Popescu *et al.* (U.S. 5,897,873). The examiner alleges that this document anticipates a complex comprising a negatively charged adjuvant electrostatically associated with a positively charged antigen to induce a CTL response. More particularly, the examiner states that:

> Popescu *et al.* clearly anticipates an immune complex comprising lipid A comprising phosphatidic acid or phosphatidyl glycerol that is electrostatically associated with a positively-charged antigen, see column 3, line 65 to column 5, line 5 and lines 35-37, column 8, lines 11-15 and claims 1-8. This complex of Popescu *et al.* also induces a CTL response, see column 2, lines 5-16.

Office Action at page 10.

The amended claims state that the organic complex comprises saponin. Accordingly, the claims clearly distinguish over Popescu *et al.*

Section 103(a) Rejection

Claims 1-11 and 17 are rejected over Cox *et al.*, *Vaccine* 15: 428 (1997), and Callahan *et al.*, *Pharmacological Res.* 8: 851 (1991). The examiner urges that

> Cox *et al.* review adjuvants and more specifically ISCOM™ complexes on page 251 and teach that these complexes induce Th1 and Th2 responses against antigens incorporated into them. Cox *et al.* do not teach the electrostatic association between the antigen and ISCOM™. However, Callahan *et al.* teach the importance of surface charge in antigen-adjuvant complexes and clearly demonstrates that there is enhanced adsorption between a positively charged antigen and a negatively charged adjuvant, see the entire reference. One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate positively charged antigens and negatively-charged adjuvants to increase adsorption into the adjuvant carrier matrix [and] would have had a reasonable expectation for increasing adsorption of positively-charged antigens into ISCOMs because both references teach that the respective adjuvants incorporate antigens into the matrix.

Applicants must emphasize, however, that the examiner's position treats the cited documents in isolation. Instead, she should consider them in the context of the prior-art teachings extant at the time of the invention.

For instance, Callahan *et al.* do teach electrostatic binding of antigen to aluminum salt adjuvants. At the time of the present invention, however, there had been no consideration whatsoever to the prospect of using the charge that exists on ISCOMATRIX as a formulation mode. Rather, the relevant prior art was directed largely to analyzing different means for modifying proteins to include hydrophobic regions such that they could be formulated into ISCOMs. For example, see Barr and Mitchell (1996), attached.

In other words, the contemporaneous literature on ISCOMs and ISCOMATRIX, which molecules are relevant to the presently claims, actually taught away from the idea of electrostatic association between antigens and ISCOMs, pointing instead toward the notion of modulating hydrophobicity. One of the advantages of the present invention is that electrostatic association provides a means of associating an antigen with a carrier, irrespective of the existence or *absence* of "appropriate" hydrophobicity. Accordingly, the skilled artisan would not have been motivated to pursue formulations based on electrostatic association.

Double Patenting Rejection

Under the doctrine of obviousness-type double patenting, the examiner has provisionally rejected claims 1-43 and 52 over claims 1-32 and 35-47 of U.S. application serial No. 09/714438. As previously noted, applicants do not acquiesce to the stated rationale for this rejection. The issue is raised provisionally, as indicated, subject to an allowance of the second application. Once allowable subject matter is indicated in this application, applicants will revisit the issue of obviousness-type double patenting, and they are amenable to employing a terminal disclaimer, should that be required.

Information Disclosure Statement

Forwarded with this response is an Information Disclosure Statement which cites references cited in supplemental search reports from the EPO in the counterpart of this case and a related case.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 25 August 2007 By S. A. Bent

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